REMARKS

Claims 1, 2, and 21, 25- 32, 34, and 37-40 are pending in the application. Claims 3-20, 22-24, 33, 35, and 36 have been canceled without prejudice. These amendments add no new matter.

Allowable Subject Matter

At page 2 of the Office Action, the Examiner stated that claims 1, 2, and 32 "seem to be free of prior art, and are allowable." In view of the amendments and arguments presented herein, applicant respectfully submits that all of the pending claims are in condition for allowance.

Objections to the Specification

On page 3 of the Office Action, the Examiner objected to the specification as containing blank spaces after "ATCC" on, e.g., pages 7-9. These blank spaces are intended to be filled when American Type Culture Collection (ATCC) deposit information for a plasmid containing CARD-14 becomes available. Prior to payment of the issue fee, applicant will either insert this deposit information or remove the blank spaces from the specification.

35 U.S.C. §112, First Paragraph (Written Description)

At pages 2-5 of the Office Action, the Examiner rejected claims 21-28 and 33-37 as allegedly containing subject matter that was not described in the specification in such a way that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The present rejection was discussed with Examiners Davis, Caputa, and Eyler during the telephone interview with the undersigned on January 15, 2004. As agreed during the interview, all of the written description rejections will be withdrawn for the reasons of record in applicant's Response to Office Action filed on June 12, 2003.

35 U.S.C. §112, First Paragraph (Enablement)

At pages 5-7 of the Office Action, the Examiner rejected claims 21-31 and 33-40 as allegedly not enabled. According to the Examiner,

> it would be undue experimentation for one of skill in the art to make the claimed invention. Thus the contemplation of using such polypeptides for screening compounds that inhibits the CARD-14-Bcl-10 interaction and thereby block cell signaling processes that result from the interaction would not obviate this rejection, since one would not know how to make such polypeptides for use as contemplated in the specification.

The Examiner stated that, for the following specific reasons, it would allegedly require undue experimentation for one of skill in the art to make the claimed polypeptides.

> Concerning the claimed polypeptide variants of SEQ ID NO:2 that bind to Bcl-10, Applicant has not shown how to make such variants. Applicant has not shown how to make the claimed variants that do not include the CARD domain, or how to change 3%, 5% or 15% at any amino acid position of SEQ ID NO:2 and still result in a polypeptide that binds to Bcl-10.
>
> Concerning claims 21-25 and dependent claims 33-34, 35-37, Applicant has not shown how to make the claimed polypeptides with any structure and function, wherein said polypeptides comprise a fragment of SEQ ID NO:2.
>
> Concerning claims 29-31, and 38-40, drawn to polypeptide variants of SEQ ID NO:2, that activates NF-kB or stimulate phosphorylation of Bcl-10, Applicant has not shown how to make such variants. Applicant has not shown how to change 3%, 5% or 15% at any amino acid position of SEQ ID NO:2 and still result in a polypeptide that activates NF-kB or stimulates phosphorylation of Bcl-10.
>
> Protein chemistry however is unpredictable, wherein change of a single amino acid could often dramatically affect the biological activity and characteristics of a protein, as taught by Burgess et al, Lazar et al, Tao et al and Gillies et al, all of record.

Claims 22-24, 33, 35, and 36 have been canceled, thereby rendering their rejection moot. Applicant respectfully traverses the remaining rejections. For the following reasons, a person of ordinary skill in the biological arts at the time of filing of the present application would have been able to make the claimed polypeptides without undue experimentation.

(i) How to Make Polypeptides Containing the Caspase Recruitment Domain (CARD) or Guanylate Kinase (GUK) Domain of CARD-14

The present application describes the identification and characterization of a protein designated CARD-14. CARD-14 has an N-terminal caspase recruitment domain (CARD; at about amino acid residues 10-116 of SEQ ID NO:2) and a C-terminal guanylate kinase domain (GUK; at about amino acid residues 826-1004 of SEQ ID NO:2) (see specification at page 18, lines 26-36; page 24, line 20; and page 26, lines 1-16). A CARD is a protein-binding module that mediates the assembly of CARD-containing proteins into apoptosis and NF-kB signaling complexes. A GUK domain is a GTP-binding domain that, together with a PDZ and an SH3 domain, is found in members of the membrane-associated guanylate kinase (MAGUK) protein family, to which CARD-14 belongs.

Claims 21 and 25 require, respectively, that the claimed polypeptide contain the amino acid residues that correspond to the CARD (claim 21) or GUK domain (claim 25) of CARD-14. Because the claimed polypeptides each contain an intact functional domain of CARD-14, the polypeptides *necessarily* retain the functional activity of the respective domain.

The CARD (about amino acids 10-116 of SEQ ID NO:2) of CARD-14 binds to the CARD of Bcl-10. Accordingly, a polypeptide containing amino acids 10-116 of SEQ ID NO:2 *necessarily* binds to Bcl-10. The CARD-containing polypeptide of claim 21 can therefore be used to screen for compounds that modulate the CARD-14-Bcl-10 interaction. The specification contains a working example of a polypeptide that contains a CARD-containing fragment (amino acids 1-118 of SEQ ID NO:2) of CARD-14 fused to a heterologous amino acid sequence for use in a mammalian two-hybrid expression assay (see specification at page 20, lines 10-31). In the working example, applicant demonstrated that the fusion polypeptide containing the CARD of CARD-14 bound specifically to the CARD of Bcl-10. Such a fusion polypeptide can be used to identify candidate therapeutic agents that inhibit the CARD-14-Bcl-10 interaction and thereby block cell signaling processes that result from the interaction.

The GUK domain (about amino acids 826-1004 of SEQ ID NO:2) of CARD-14 is expected to be a GTP-binding domain. Accordingly, a polypeptide containing the GUK domain

of CARD-14 is expected to *necessarily* bind to GTP. The polypeptide of claim 25 can therefore be used to screen for compounds that modulate the GTP-binding ability of the GUK domain of CARD-14 (see specification at pages 67, lines 20-24). Nucleotide binding assays are well known to those of skill in the biological arts. Compounds identified by such screens can be used to modulate CARD-14-mediated signal transduction and therefore modulate, for example, CARD-14 mediated apoptosis and/or inflammation.

In light of these comments, applicant respectfully submits that the specification combined with the level of skill in the art at the time of filing of the present application enabled the skilled artisan to make the claimed polypeptides without undue experimentation.

(ii) How to Make Polypeptide Sequence Variants CARD-14

The specification includes working examples that characterize the role of CARD-14 in cell signaling pathways involved in apoptosis and/or inflammation. In particular, applicant demonstrated that: (1) CARD-14 selectively binds to the CARD of Bcl-10, a signaling protein that activates NF-kB through the IkB kinase complex in response to upstream stimuli; (2) CARD-14 stimulates the activation of NF-kB; and (3) CARD-14 induces phosphorylation of Bcl-10. These findings indicate that CARD-14 functions as an upstream activator of Bcl-10 and NF-kB signaling.

Claims 26-31 and 38-40 are drawn to polypeptides that (a) contain an amino acid sequence that is at least 85% identical to the sequence of SEQ ID NO:2, and (b) have one of the following CARD-14 functional activities described in the working example section of the application: (i) bind to Bcl-10; (ii) activate NF-kB; or (iii) stimulate phosphorylation of Bcl-10.

It is well within the grasp of the biologist of ordinary skill to prepare a polypeptide that is at least 85%, at least 95%, or at least 98% identical to the CARD-14 sequence of SEQ ID NO:2. For example, the specification describes standard mutagenesis methods that can be used produce combinatorial libraries expressing variants of CARD-14 (see specification at page 41, line 20, to page 42, line 30). Furthermore, the specification instructs that conservative amino acid substitutions can be made in a CARD-14 protein so as to reduce the likelihood that a given

amino acid change will result in a loss of CARD-14 function (see specification at page 32, lines 8-34).

In addition to being able to readily produce CARD-14 sequence variants having at least 85% identity with SEQ ID NO:2, it would have required no undue experimentation for the skilled artisan to identify those variants that retain the specific CARD-14 functional activity recited in the claims. By using the assays described in the specification, the skilled artisan would have been able to determine whether a given CARD-14 sequence variant binds to Bcl-10, activates NF-kB, and/or stimulates phosphorylation of Bcl-10. Readily screenable assays that permit the skilled artisan to determine whether a given CARD-14 variant possesses the functional activity required by claims 26-31 and 38-40 are described in the specification, as follows: (1) claims 26-28 (assays for detecting CARD-14 binding to Bcl-10; page 20, line 9, to page 22, line 9; Figures 6 and 7); (2) claims 29-31 (assays for detecting CARD-14 activation of NF-kB; page 23, line 22, to page 24, line 15; Figures 9A-9C); and (3) claims 38-40 (assays for detecting CARD-14 stimulation of Bcl-10 phosphorylation; page 22, line 11, to page 23, line 20; Figure 8).

The Examiner asserted that "[p]rotein chemistry however is unpredictable, wherein change of a single amino acid could often dramatically affect the biological activity and characteristics of a protein." To support this assertion, the Examiner cited four references which analyzed the effects of selected point mutations on the functional activity of Heparin-Binding Growth Factor-1 (Burgess et al), TGF-alpha (Lazar et al.), or immunoglobulins (Tao et al. and Gillies et al.).

These references' analyses of the functional importance of selected amino acid residues fail to negate the patentability of the claimed polypeptides. Although it is possible in certain cases to abolish the functional activity of a protein by mutating a critical amino acid residue, this does not mean that one of ordinary skill cannot nonetheless readily make functional analogs of a given protein (e.g., CARD-14) without undue experimentation. In fact, as detailed in the publication of Bowie et al. (1990) Science 247:1306-10 (enclosed as "Exhibit A"), "proteins are surprisingly tolerant of amino acid substitutions" (Exhibit A at page 1306, col.2, lines 12-13).

Exhibit A cites as evidence of this assertion a study carried out on the *lac* repressor that found that of approximately 1500 single amino acid substitutions at 142 positions in the protein, "about one-half of all substitutions were phenotypically silent" (Exhibit A at page 1306, col. 2, lines 14-17). Thus, one can expect, based on Exhibit A's disclosure, that a significant percentage random substitutions in a given protein will result in mutated proteins with full or nearly full activity. These are far better odds than those at issue in *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988), in which the court found that screening many hybridomas to find the few that fell within the claims was not undue experimentation. The question is not whether it is possible to abolish activity of a given protein by introducing a point mutation, but rather whether one of ordinary skill can produce, without undue experimentation, mutants in which the activity is not abolished.

Based on Exhibit A's disclosure, one would predict that even random substitution of amino acid residues in CARD-14 will result in a large pool of mutants having full or partial CARD-14 activity (i.e., a CARD-14 functional activity recited in the claims). Furthermore, as detailed herein, the specification amply teaches the skilled artisan how to select those mutants having the activity required by the claims. In light of these comments, applicant submits that one of ordinary skill in the art would have been able, at the filing of the present application, to make and use the claimed polypeptides without undue experimentation. Accordingly, applicant requests that the Examiner withdraw the rejection.

CONCLUSION

Applicant asks that all claims be allowed in view of the amendments to the claims and the remarks contained herein.

Enclosed is a Petition for Two Month Extension of Time and a $420 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 07334-142001.

Respectfully submitted,

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